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Included in this report are summaries of recent information on terminal residues of nine methyl and dimethyl carbamates and a section on metabolic activation reactions of derivatized carbamates.

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TERMINAL RESIDUES OF CARBAMATE INSECTICIDES

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Three reviews of carbamate metabolism have appeared recently (1-3). One general review covered the degradation in soil and by soil microorganisms (2) and the third review addressed the specific topic of derivatized carbamate insecticides (3). Many of the points noted in these reviews have been covered in previous reports.

Included in this report are summaries of recent information on terminal residues of nine methyl and dimethyl carbamates and a section on metabolic activation reactions of derivatized carbamates.

CARBARYL

Further studies on the metabolic fate of carbaryl (1-naphthyl N-methylcarbamate), using an isolated rabbit lung perfusion technique, showed a similar pattern of metabolism as has been described in detail in previous years. Simple diffusion was responsible for rapid uptake, 26% in 15 minutes, and oxidative and/or hydrolytic pathways resulted in the presence of 4-hydroxycarbaryl and α-naphthol (4,5). Studies on the breakdown of α-naphthol by a fungal preparation showed evidence of polymerization. An extracellular phenol oxidase was believed responsible for the formation of dimeric, trimeric, tetrameric and pentameric derivatives (6). The specificity of the reaction was not limited to α-naphthol as a series of different phenols showed similar results.

o-(SEC-BUTYL)PHENYL N-METHYLCARBAMATE

In a series of papers, the metabolic fate of o-(sec-butyl)phenyl N-methylcarbamate was examined in rice plants, microbial organisms and soil (7-11). Using a ^{14}C-labeled product (carbon atom 1 of the side chain), the carbamate was shown to be rapidly absorbed and translocated within 9 days of treating rice. After 9 days, the major residue was believed to be volatile compounds. A series of 15 metabolites were detected with the major products being hydroxylated derivatives of the carbamate and conjugates. o-(sec-Butyl)phenyl N-methylcarbamate, when applied to soil, was rapidly degraded through oxidative and conjugative pathways. The major metabolic products identified were 2-(1-acetylethyl)phenyl N-methylcarbamate, the parent carbamate and its phenol, ring hydroxylation products and conjugates of the parent carbamate.

In studies with Aspergillus, a series of metabolites was identified including: o-(sec-butyl)phenol, o-(sec-butyl)phenyl carbamate, the N-hydroxymethylcarbamate, o-(1-methyl-2-oxopropyl)phenyl N-methylcarbamate, o-(1-hydroxy-1-methylpropyl)phenyl N-methylcarbamate, threo-(and erythro)-o-(2-hydroxy-1-methylpropyl)phenyl N-methylcarbamate, and the 3-hydroxy derivative of the parent molecule. Thus, as might be expected, the alkyl sidechain, the N-methyl moiety and the aromatic ring were subject to oxidative metabolism followed by conjugation.

CARBOFURAN

Following foliar treatment of strawberries with carbofuran (2,3-dehydro-2,2-dimethyl-7-benzofuranyl N-methylcarbamate), metabolites identified were oxidative products previously reported, 3,7-diol and 3-oxocarbofuran (12). Following field treatment of corn, 50-80% of the carbamate recovered was the 3-hydroxycarbofuran. Conjugates of 3-hydroxy-, 3-oxo- and carbofuran were also found (13). Samples of alfalfa hay treated with carbofuran and exposed to drying conditions in sunlight, UV light and air in the dark revealed that

8o-9o% of the residue was lost within 1o days post treatment. The levels of 3-hydroxy-, 3-oxocarbofuran, 3,7-diol and 3-oxo-7-phenol increased in all samples. 3-Hydroxycarbofuran increased most dramatically in the dark-drying experiment (14).

THIOFANOX

Thiofanox [3,3-dimethyl-1-(methylthio)-2-butanone O-(methylaminocarbonyl)-oxime] was stable in acidic and neutral solutions. At pH 1o, it underwent a two-step oxidation to its sulfone derivative with subsequent hydrolysis of the sulfone (19). When thiofanox was applied to potato crops at recommended (USA and Canada) treatment rates, residues found in the tubers were removed by (a) storage, (b) baking and frying and (c) boiling. Terminal residues following the processing were hydrolysis products of the oxime carbamate (2o). Chromatographic separation and detection procedures for thiofanox and its metabolites (sulfoxide and sulfone of the carbamate and oxime) by TLC were reported (21).

ALDICARB

Soil degradation studies using aldicarb [2-methyl-2-(methylthio)propanal O-(methylaminocarbonyl)oxime] labeled at the S-methyl, N-methyl and tertiary carbon showed that up to 83% of the applied radiolabel was recovered as $^{14}CO_2$ from the S-methyl-^{14}C-aldicarb. From the labeled N-methyl and tertiary carbon positions 61 and 45%, respectively, were collected as $^{14}CO_2$. Aldicarb sulfoxide and sulfone were the major metabolites soluble in organic solvents. The maximum residue of intact carbamate was estimated at 4-7% of the applied dose (15). Aldicarb applied to soil columns proved to be very mobile in the soil as were the sulfone and sulfoxide oxidation products. Aldicarb conversion followed first order kinetics with a half-life of about 2 days. Decomposition of the sulfoxide was much slower with a half-life of 12-23 days (16). Homogenates of roots of several plants were found to metabolize aldicarb to the sulfoxide (17). The isolated enzyme responsible for the sulfur oxidation was inhibited by a multitude of sulfur-containing molecules apparently competing in the oxidative reaction.

METHOMYL

The metabolism of methomyl [Methyl N-(methylcarbamoyloxy)thioacetimidate] in rats, plants, and soil was reviewed and compared to that noted with aldicarb (18). Methomyl was rapidly converted to CO_2 and acetonitrile without the appearance of the sulfoxide or the sulfone. In soils, methomyl was hydrolyzed to the corresponding oximino compound, followed by total decomposition to CO_2 without acetonitrile formation.

PROMECARB

Promecarb (3-methyl-5-isopropylphenyl N-methylcarbamate) when orally administered to rats was rapidly eliminated primarily in the urine. Within 3 days post treatment over 9o% of the administered dose was eliminated generally as unidentified water soluble components. A totel of nine organosoluble metabolites were observed. Promecarb and the phenol, both free and conjugated, were present in small quantities (ca. 3%) in the urine. The rest of the isolated products were unidentified (22).

AZAK

The phototransformation of Azak (2,6-di-t-butyl-4-methylphenyl N-methylcarbamate) produced only trace amounts of the photo-Fries product. The decarbamylated product was observed, but the ortho- and para-directed products were not seen. After 3o hours UV exposure in ethanol, 52% of the Azak had decomposed. Four percent was accountable as photo-Fries product (23).

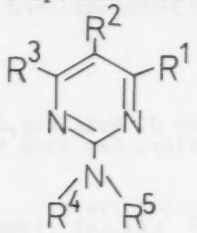
PIRIMICARB

Pirimicarb [2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl N,N-dimethylcarbamate] is rapidly absorbed, distributed, metabolized and excreted in mammals. In studies with dogs and rats administered ^{14}C-pirimicarb (labeled in ring or carbonyl positions), excretion was rapid, primarily in the urine. From 86 to 94% of the ring-labeled dose was recovered (79-88% in urine, 6-7% in feces). With carbonyl-labeled pirimicarb, 15-26% of the dose administered to dogs was recovered, predominantly in urine. The unrecovered product

$(^{14}CO)_2$ was believed to be eliminated rapidly in expired air as suggested by studies in which rats were administered carbonyl-^{14}C-pirimicarb by gavage or intraperitoneal injection. Over 50% of the dose administered to rats was expired as $^{14}CO_2$ within 5 hours following administration by either route (24). Studies on the absorption, tissue distribution and excretion in rats following oral or intraperitoneal injection again suggested a pattern of rapid absorption, degradation of the carbonyl group to CO_2 and minor(15%) elimination of intact carbamate in the urine. There was essentially no storage in the body of rats sacrificed 8 days after treatment (25). Measurement of abdominal fat from rats administered pirimicarb and sacrificed 24 hours after treatment (either a single application or up to 4 daily treatments) resulted in no accumulation of pirimicarb in adipose tissue (26).

Pirimicarb administered to a lactating cow at a dose of 1 mg/kg was rapidly excreted, again primarily in the urine (96%) and feces (4%). A trace of material (less than 0.3% of the recovered dose) was observed in milk with a maximum occurring within one hour of treatment (27).

The urinary metabolites from rats and dogs administered pirimicarb by gavage or intraperitoneal injection were basically the same suggesting a similar metabolic route. The major metabolites were identified as phenolic components of pirimicarb with modifications of the alkyl constituents of the aromatic moiety. A complete metabolic scheme for the degradation of pirimicarb can encompass any of 5 alkyl groups although only a few of the many theoretical compounds have been isolated.



R^1	R^2 - R^5	
$C(O)NCH_3CH_3$	CH_3	(pirimicarb)
$C(O)NCH_3CH_2OH$	CH_2OH	
$C(O)NHCH_3$	H	
$C(O)NHCH_2OH$		
OH		

As expected, oxidative and hydrolytic mechanisms act on various components of the molecule, i.e., the carbonyl ester, the $N(CH_3)_2$ group of both the ring and carbamate moiety and the CH_3 groups at positions 5 and 6 of the pyrimidine nucleus. Quantitative analysis of isolated metabolites from urine of rats, dogs and a lactating cow show essentially the same pattern of metabolism. The following four metabolites were recovered from urine:

Metabolite	% of Administered Dose		
	Rat	Dog	Cow
2-dimethylamino-4-hydroxy-5,6-dimethylpyrimidine	16.3	6.4	10
4-hydroxy-5,6-dimethyl-2-methylaminopyrimidine	40.9	20.7	41
2-amino-4-hydroxy-5,6-dimethylpyrimidine	12.9	16.5	21
4-hydroxy-6-hydroxymethyl-5-methyl-2-methylaminopyrimidine	5.7	1.8	--

Conjugation of phenolic products was not evident in these studies. There were few aglycones recovered following treatment of urinary products with glucuronidase and chromatographic characterization of organic soluble products. It was assumed that the metabolites predominated in the tautomeric pyrimidone configuration restricting conjugation. Small quantities of the phenol were recovered as conjugates, but the major products were eliminated as unconjugated metabolites.

Metabolism in plants occurred by photochemical reactions on the leaf surface or by metabolic processes within the leaf. Two products were identified which were not found in dog or rat urine. These were the 2-formylmethylamino derivative and the 2-methylamino derivative, each containing the intact carbamate. While these were isolated from plants and not animals, the proba-